FORMULATION AND EVALUATION OF SUSTAINED RELEASE METOCLOPRAMIDE HYDROCHLORIDE MATRIX TABLET

A Dissertation work submitted to

THE TAMILNADU Dr. M.G.R.MEDICAL UNIVERSITY, CHENNAI

In partial fulfillment of the requirements for the award of degree of

MASTER OF PHARMACY

IN

PHARMACEUTICS

BY

REG. NO: 26105110

Under the guidance of

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CERTIFICATE

This is to certify that the investigation in this thesis entitled **FORMULATION AND EVALUATION OF SUSTAINED RELEASE METOCLOPRAMIDE HYDROCHLORIDE MATRIX TABLET** submitted to the Tamil Nadu Dr. M.G.R Medical University, Chennai, for the partial fulfillment of the award of degree of **Master of Pharmacy** in **Pharmaceutics,** was carried out by **Regd. No. 26105110** in the department of pharmaceutics, **The Erode College of Pharmacy and Research Institute**, **Erode 638112**, under my guidance and supervision.

This work is original and has not been submitted in part or full to any other degree or diploma of this or any other university.

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ENDORSEMENT BY THE PRINCIPAL

This is to certify that the investigation described in this dissertation entitled "**FORMULATION AND EVALUATION OF SUSTAINED RELEASE METOCLOPRAMIDE HYDROCHLORIDE MATRIX TABLET" ,** submitted in Partial fulfillment of the requirements for the Degree of **Master of Pharmacy** in **PHARMACEUTICS** was carried out in the laboratories of The Erode College of Pharmacy and Research Institute, Erode by **Reg. No. 26105110** under the guidance of **Dr. V. GANESAN, M. Pharm., Ph.D., Principal, The Erode College of Pharmacy and Research Institute**, **Erode 638112**, during the academic year 2011-2012.

DECLARATION

The research work embodied in this dissertation entitled **FORMULATION AND EVALUATION OF SUSTAINED RELEASE METOCLOPRAMIDE HYDROCHLORIDE MATRIX TABLET** was carried out by me in the **Department of Pharmaceutics**, **The Erode College of Pharmacy & Research Institute, Erode**, under the direct supervision of **Dr. V. GANESAN, M. Pharm., Ph.D., Principal,** Dept. of Pharmaceutics, The Erode College of Pharmacy & Research Institute, Erode – 638 112.

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Abbrevations

λ_{max}	=	Wavelenght of maximum absorption
Cm	=	Centimeter
CAP	=	Cellulose Acetate Phatlate
Conc.	=	Concentration
Fig.	=	Figure
FTIR	=	Fourier Transform Infrared
Gm	=	Gram
GI	=	Gastro Intestinal
HCL	=	Hydrochloric acid
HPMC	=	Hydroxypropyl methyl cellulose
IPA	=	Isopropyl alcohol
I P	=	Indian Pharmacopoeia
I R	=	Infrared

Kg	=	Kilogram
MCC	=	Micro crystalline cellulose
Mm	=	Millimeter
Mg	=	Milligram
Ml	=	Milliliter
MCP	=	Metoclopramide
Ng	=	Nanogram
PEG	=	Poly ethylene Glycol
RH	=	Relative Humidity
RS	=	Reference Standard
SR	=	Sustained Release
USP	=	United States Pharmacopoeia
UV	=	Ultraviolet

CONTENTS

ABSTRACT

Metoclopramide hydrochloride (MCP) is commonly used for the management ofgastrointestinal disorders. Frequent administration and the undesired side effects (extrapyramidal symptoms) of the drug on the central nervous system due to the fluctuationsof its plasma concentrations may lead to patient incompliance, and hence, impropertherapy. Therefore, the present work will be devoted to formulate the drug in sustainedrelease formulations. Metoclopramide hydrochloride MCP was incorporated in 7 formulae containing differentpolymers and/or different polymer ratios. These polymers were hydroxypropylmethylcellulose (HPMC), Sodium carboxymethylcellulose (CMC).Mannitolwas added to f4-f7 formulae in different amounts in order tosoften and/or disintegrate the tablets. Both direct compression and granulationtechniques were used to prepare the tablets. The physical properties were found to besatisfactory for all the formulae. The dissolution profiles of the tablets were constructedusing the change-over method. The drug release involved a combination of bothdiffusion and polymer-chain relaxation mechanisms. The time required to release 50%of MCP ranged from 1.2 to more than 8 hours. Direct compression technique produced sufficient sustaining of the drug release.

Keywords: Metoclopromide HCL,sustained release. HPMC, SCMC.

INTRODUCTION

Oral drug delivery has been known for decades as the most widely utilized route of administered among all the routes that have been employed for the systemic delivery of drug via various pharmaceutical products of different dosage forms. The reasons that the oral route achieved such popularity may be in part attributed to its ease of administration and the belief that oral administration of the drug is well absorbed[1].

All the pharmaceutical products formulated for systemic delivery via the oral route of administration irrespective of the mode of delivery (immediate sustained or controlled release) and the design of dosage forms (either solid dispersion or liquid) , must be developed within the intrinsic characteristics of GI physiology , pharmacokinetics , pharmacodynamics and formulation design is essential to achieve a systemic approach to the successful development of an oral pharmaceutical dosage form.[2,3]

RATIONAL OF SUSTAINED AND CONTROLLED DRUG DELIVERY

The basic rational for controlled drug delivery is to alter the pharmacokinetic and pharmacodynamics of pharmacological active moieties by using novel drug delivery system or by modifying the molecular structure and physiological parameters inherent in the selected route of administration. It is desirable that the duration of drug action becomes more a design property of a rate controlled dosage form and less or not at all a property of the drug molecules properties, inherent kinetics. Thus optional design of controlled release systems necessitates a thorough understanding of the pharmacokinetics and pharmacodynamics of the drugs.

SUSTAINED AND CONTROLLED RELEASE DRUG DELIVERY SYSTEMS

Over the Past 30 years, as the expense and complications involved on marketing new drug entities have increased , with concomitant recognition of the therapeutic advantages of controlled drug delivery , greater attention has been focused on development of sustained or controlled release drug delivery systems. The attractiveness of these dosage forms is due to awareness to toxicity and infectiveness of drugs when administered or applied by conventional method in the form off tablets, capsules , injectables , ointments etc. Usually conventional dosage form produces wide- ranging fluctuation in drug concentration in the bloodstream and tissues with consequent undesirable toxicity and poor efficiency. These factors as well as factors such as repetitive dosing and unpredictable absorption lead to the concept of controlled delivery systems. The goal in designing sustained or controlled delivery system is to reduce the frequency of the dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or providing uniform drug delivery. So sustained release dosage form is a dosage form that release one or more drugs continuously in predetermined pattern for a fixed period of time, either systematically or to a specified target organ. Sustained release dosage forms provide a better control of plasma drug level, less dosage forms provide a better control of plasma drug levels, less dosage frequency, less side effect, increased efficiency and constant delivery.

2.1 Terminology[4]

Modified release delivery system may be divided conveniently into four categories.

1. delayed release
2. sustained release

- controlled release
- extended release

Delayed release:

These systems are those that use repetitive, intermittent dosing of a drug from one or more immediate release units incorporated into a single dosage form. Examples of delayed release systems include repeated action tablets and capsules and enteric-coated tablets where timed to release is achieve by a barrier coating.

Sustained release:

These systems include any drug delivery system that achieves slow, release of drug over an extended period of time.

Controlled release:

These system also provide a slow release of drug over an extended period of a time and can provide some control, whether this be of a temporal or spatial nature, or both, of drug release in the body, or in other words, the system is successful at maintaining constant drug levels in the target tissue or cells.

Extended Release:

Pharmaceutical dosage forms that release the drug slower than normal manner of predetermined rate & necessarily reduce the dosage frequency by two folds.

Site specific targeting drug delivery:

These systems refer to targeting of a drug directly to a certain biological location. In this case the target is adjacent to or in the diseased organ or tissue.

Receptor targeting Drug Delivery:

These systems refer to targeting of a drug directly to a certain biological location. In this case the target is the particular receptor for a drug within an organ or tissue.

Site specific targeting & receptor targeting systems satisfy the spatial aspect of drug delivery & are also considered to be controlled drug delivery system.

2.2 Release Rate and Dose Consideration:

As already mention, conventional dosage forms include solutions, Capsules, tablets, emulsions, aerosols, foams, ointment & suppositories. These dosage forms can be release their active ingredients into an absorption pool immediately.

Kr KaKe

Dosage form -----→ Absorption pool ----→ Target area----→Elimination

Drug Release absorption

Kr = First order rate constant for drug release.

Ka = First order rate constant for drug absorption.

Ke = First order rate constant for overall drug elimination.

For immediate release dosage forms Kr >>> Ka or alternatively absorption of drug across a biological membrane is the rate- limiting step in delivery of the drug to its target area.

For non-immediate release dosage forms , Kr <<< Ka , that is, release of drug from the dosage form is the rate limiting step. This cause the above kinetics scheme to reduce to .

Kr Ke

Dosage form ----------→ Target Area ----------→elimination

Drug Release

Thus, the effort to develop a no immediate release delivery system must be directed primarily by altering the release rate by affecting the value of Kr.

The ideal goal of designing sustained –release system is to deliver drug to the desired site at a rate according to needs of the body,i.e., a self regulated system based on its feedback control the release system but this is a difficult assignment.

The pivotal question is at what rate should be drug delivered to maintain a constant blood drug level? This constant rate should be analogous to that achieved by continuous intravenous infusion where a drug is provided to the patient at a constant rate s just equal to its rate of elimination. This implies that the rate of delivery must be independent on the amount of drug remaining in the dosage form & constant over time. That is , release from the dosage form should follow Zero-order kinetics, as shown by,

Kro = Rate in=Rate out= Ke Cd Vd

Where

Kro= Zero order rate constant for drug release(amount/time)

Ke = First order rate constant for overall drug elimination(time")

Cd= Desired drug level in the body(amount/volume)

Vd = Volume space in which the drug is distributed.

For many drug, more complex elimination kinetics and other factors affects their deposition. This is then affects the nature of release kinetics necessory to maintain a constant drug level. It is important to recognize that while Zero - order release may be desirable theoretically; non Zero-order release may be equivalent clinically to constant release in many cases. Aside from the extent of intra and inter subject variation is the observation that for many drugs, modest changes in drug tissue levels do not result in an improvement in clinical performance. Thus, a constant drug level may be indistinguishable clinically from a constant drug level.

To achieve a therapeutic level promptly and sustain the level for a given period of time, the dosage generally consists of two parts: an initial primary dose, Di, that releases drug immediately and a maintenance or sustaining dose, Dm.

The total dose, W, thus required for the system is

$W = Di |+ Dm$

For a system in which the maintenance dose releases the drug by a zero order process for a specified period of time, the total dose is

$W = Di + Kr0\ Td$

Kr0= Zero order rate constant for drug release

Td = Total time desired for a sustained release from one dose.

If the maintenance dose begins to release the drug at the time of dosing (t=0), it will add to that which is provided by the initial dose, thus increasing the initial drug level. In this case a correction factor is needed to account for the added drug from the maintenance dose.

$W=Di + Kr0\ Td – Kr\ 0\ Kr\ 0Tp$

The correction factor , $Kr\ 0Tp$ is the amount of drug provided during the period from t=0 to the time of the peak drug level , Tp No correction factor is needed if the dosage form is constructed in such a fashion that the maintenance dose not begin to release drug until time Tp.

Suitable combination of the initial dose and maintenance dose that releases its drug can be obtained satisfactorily in approximation of a constant drug level by a first order process.

The total dose for such a system is

$W=Di +(KeCd/Kr)Vd$

Kr = first order drug release constant (time 1)

If the maintenance dose begins releasing drug at t = 0, a correction factor is required just as it was in the zero order case. The correction expression in this case

$W= Di +(KeCd/Kr)Vd-DmKeTp$

To maintain drug blood levels within the therapeutic range over the entire time course of therapy, most sustained release drug delivery systems are ,like conventional dosage forms,administred as multiple rather than single doses. For an idel sustained– release system that releases drug by zero- order kinetics, the multiple dosing regimens is analogous to that used for a constant intravenous infusion. For those sustain-release systems having release kinetics other than zero-order, the multiple dosing regimens are more complex.

2.3Oral Sustained and controlled Release System:

- Total 5 types of oral controlled release systems are available.
- Dissolution controlled release system.
- Diffusion controlled system.
- Bioerodible and combination diffusion and dissolution system.
- Osmotically controlled release system.
- Ion exchange systems.

2.3.1 Dissolution controlled release system: [6]

A drug with a slow dissolution rate will sustain release rate of the drug from the dosage form. Here the rate –limiting step is dissolution.This is true, sustain release preparation of drugs could be made by decreasing their rate of dissolution. These approaches are achieved by preparing appropriate salts or derivatives, coating the drug with a slow dissolving material or incorporating it into a tablet with a slowly dissolving carrier.

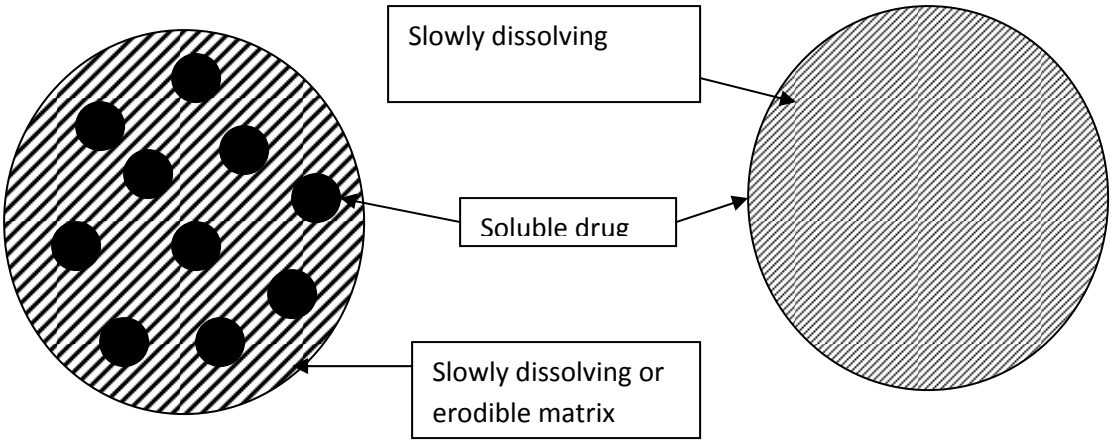


Figure .1. Schematic representation of dissolution controlled release system

(a) matrix system ,

(b) coated / encapsulated system

Dissolution controlled systems can be made either by rate controlling coats or by administering the drugs as a group of beads that have coating of different thickness. In first case if the outer layer is a quickly releasing bouls of drug, initial levels of drug in the body can be quickly established with plused intervals.

In second case since the beads have different coating thickness; there release will occur in progressive manner. Those with the thinnest layer will provide the initial dose and the maintenance of drug levels at later times will be achieved from those with thicker coating. The Noyes – Whitney equation, describes this dissolution process at steady state

$$\frac{Dc}{Dt} = KD\,A\,(Cs-C) = \frac{D}{h}\,A\,(Cs-C)$$

Where,

Dc/dt = dissolution rate

Kr = dissolution rate constant.

D = diffusion coefficient

Cs = Saturation solubility of the solid.

C = Concentration of solute in the bulk solution.

The above equation predicts that the rate release can be constant only if the following parameters are constant.

a) Surface area

b) Diffusion coefficient

c) Diffusion layer thickness

i. Concentration difference.

But these parameters are not easily maintained constant, especially surface area. For spherical particles, the change in surface area can be related to the weight of the particle that is under assumption of sink conditions, above equation can be rewritten as cube root dissolution equation.

$$W0^{1/3} - W^{1/3} = KDt$$

Where,

Kd = cube root dissolution rate constant

Wo = Initial weight

W = weight of the amount remaining at time t

2.3.2 Diffusion systems:

In this system release rate of a drug being dependent on its diffusion through an inert membrane barrier. Usually, this barrier is an insoluble polymer , it's again having two subclasses.

a) Reservoir devices
b) Matrix devices.

a) Reservoir devices:

Reservoir devices are characterized by a core of drug, the reservoir, surrounded by a polymeric membrane and also the nature of the membrane determines the rate of release of drug from the system.

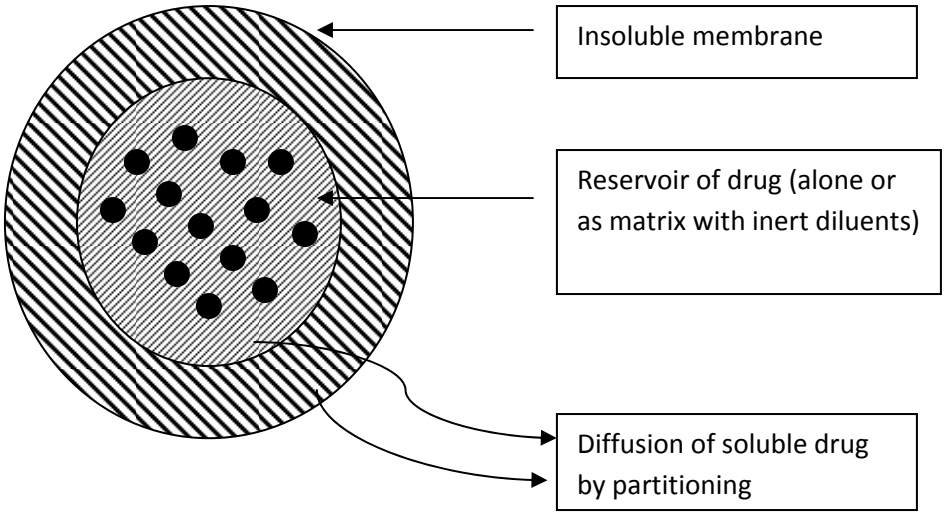


Figure 2.Drug release of diffusion across the insoluble membrane of

Reservoir device

The process of diffusion is described by Ficks equation. This equation states that the amount of drug passing across a unit area is proportional to the concentration differences across that barrier.

The equation is given as

$J = D dc/dx$……(1)

Where 'J' given in units of amount/area-time, 'D' is the diffusion coefficient of the drug in the membrane (Area/time), dc/dx represents the rate of change in concentration 'C' relative to a distance 'X' in the membrane.

Equation (1) can be integrated and simplified to give.

$J = DK \quad C/d \ldots \Delta \ldots\ldots (2)$

Where

K = Partition co-efficient

c = Concentration difference across the membrane.

d = Thickness of the diffusion layer.

In the equation (2) it is assumed that "D" and 'k' are constant.

Drug release will vary, depending on the geometry of the system 6 ..The Simplest system to consider is that of a slab, where drug release is from only one surface. In this case equation (2) can be written as

$$\frac{dMt}{dt} = \frac{ADK\ C}{d} \text{----------(3)}$$

Where

'Mt' is the mass of drug released after time't'

d Mt /dt the steady – state release rate at time 't' and

'A' the surface area of the device.

The left side of equation (3) represents the release rate of the system. A true controlled release system with a zero –order rate can be possible if all the variables on the right side of equation (3) remain constant. But it is very difficult to maintain all the parameters constants. Again depending on the device diffusion systems can provide constant release at steady state. For reservoir

devices, a system *that is* used relatively soon after construction will demonstrate a large time in release, since it will take time for

the drug to diffuse from the reservoir to the membrane surface. On the other hand, systems that are stored will demonstrate a burst effect, since, on standing the membrane becomes saturated with available drug. The magnitude of these effects is dependent on the diffusing distance (i.e. the membrane thickness).

Advantages:

i) This device can offer zero-order release of the drug.
ii) Kinetics of a particular drug can be controlled by changing the characteristics of the polymer to meet the particular therapeutic conditions.

Disadvantages:

i) System must be physically removed from implant sites.
ii) Difficult to deliver high molecular weight compounds.
iii) Generally increased cost per dosage unit.
iv) Potential toxicity if system fails.

a) Matrix devices:

Matrix devices consist of drug dispersed homogeneously throughout a polymer matrix, in the model, drug in the outside layer exposed to the bathing solution when it is dissolved first and then diffuses out of the matrix. This process continues with the interface between the bathing solution and the solid drug moving toward the interior. For this system rate of dissolution of drug particles within the matrix must be much faster than the diffusion rate of the dissolved drug leaving the matrix.`

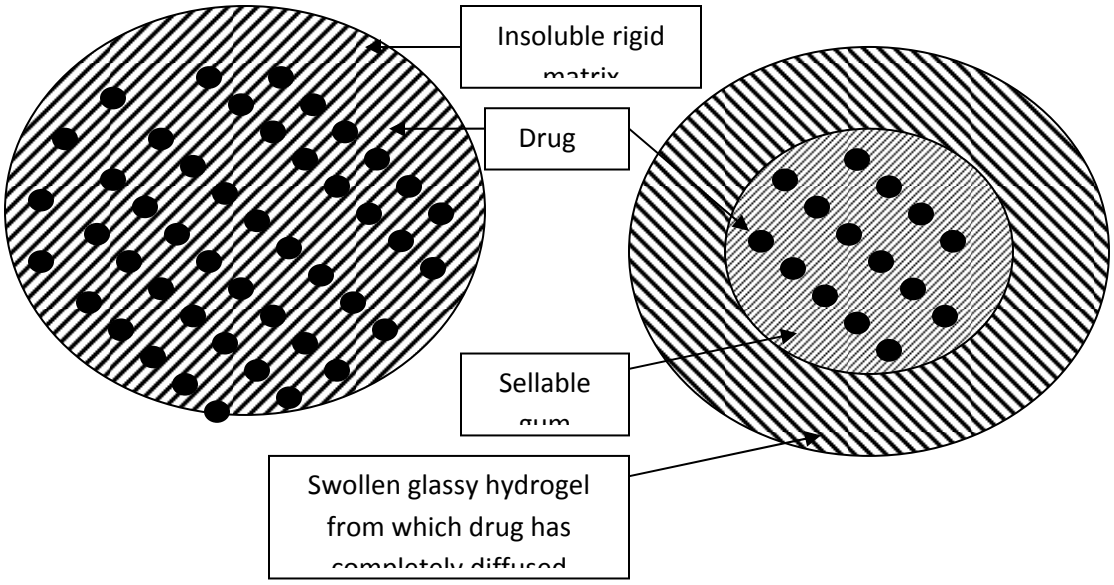


Figure.3. Diffusion controlled devices---(a)rigid matrix , and (b) swellable matrix.

The rate of release of drugs dispersed in an inert matrix system , have been derived by Higuchi.

$dM / dh = Codh - Cs/2$. –(1)

Where,

dM = Change in the amount of drug released per unit area.

dh = change in the thickness of the zone of matrix that has been depleted of

drug.

Co = total amount of drug in a unit volume of the matrix.

Cs = saturated concentration of the drug within the matrix.

From diffusion theory,

$dM = (DmCs/h). dt$ ----------(2)

Where,

Dm is the diffusion coefficient in the matrix

equation (1) and (2) integrating and solving for 'h' gives.

$M = [(CsDm2C0-Cs)\ t]^{1/2}$ ----------(3)

When amount of drug is in excess of the saturation concentration that is Co>> Cs

$M = [2CsDmCot]^{1/2}$ ----------(4)

Equation (4) indicates that the amount of drug released is a function of the square root of time.

The drug release from a porous or granular matrix can be described by

$M = (Ds.\ Ca\ \{P/T\}\ [2Co - Pca]t)^{1/2}$

Where

P = porosity of the matrix.

T = tortuosity

Ca = solubility of the drug in the release medium

D5 = diffusion coefficient in the release medium.

The system is slightly different from the previous matrix system in that the drug is able to pass out of the matrix through fluid filled channels and does not pass through the polymer directly

Advantages of matrix diffusion system:

i) Easier to produce that reservoir devices.

ii) Can deliver high molecular weight compounds

Disadvantages of matrix diffusion system:

i) Cannot obtain zero order release.

ii) Removal of remaining matrix is necessary for implanted system.

2.3.3. Bioerodible and combination diffusion and dissolution systems[7,8,9]

Therapeutic systems are not only dependent on either dissolution or diffusion system. In practice, the dominant mechanism for release will be either dissolution rate limited or diffusion controlled Bioerodible devices constitute a group of system for which release characteristics are complex. The mechanism of release from simple erodible slabs, cylinders and spheres can be described by following mathematical model.

$Mt/M = 1-(1-Kot/Coa)^n$

Where,

Mt = Mass of drug release at time t

M = Mass release at infinite time

a = Radius of sphere or cylinder or the half height of a slab.

n = 3 for a sphere, 2 for a cylinder and 1 for a slab.

This system is the combination of both diffusion and dissolution of matrix material and the drug. Drug not only can diffuse out of the dosage form but the matrix itself undergoes a dissolution process.

The complexity of the system arises from the fact that as the polymer dissolves; the diffusion path length of the drug may change. This usually results in a moving boundary diffusion system. Zero order release can occur only if surface erosion occurs and surface area does not change with time.

An advantage of such a system is that the bioerodible property of the matrix does not result in a host matrix. The disadvantage of these matrix systems is that release kinetics is often hard to control.

Another method for the preparation of bioerodible system is to attach the drug directly to the polymer by a chemical bond. Generally drug is released from the polymer by hydrolysis or enzymatic reactions.

Advantage of such system is control of the rate of release somewhat easier. Another advantage of the system is the ability to achieve very high drug loading.

Third type is the swelling controlled matrix. Here the drug is dissolved in the polymer, but instead of an insoluble or eroding polymer. Swelling of the polymer occurs. This allows entrance of water, which causes dissolution of the drug and diffusion out of the swollen matrix. In these systems the release rate is highly dependent on the polymer swelling rate, drug solubility and the amount of soluble fraction in the matrix. This system usually minimizes burst effects, since polymer swelling must occur before drug release.

2.3.4. Osmotically controlled system:

In these systems, osmotic pressure provides the driving force to generate controlled release of drug. In this system a tablet containing a core of drug surrounded by a semipermiable membrane, which is permeable to water, but not to drug. When this device is exposed to water or any body fluid, water will flow into the tablet owing to the osmotic pressure difference. The rate of flow , dv/dt, of water into the device can be represented by as.

$$Dv/dt = AK/h \ (\ T - P) \qquad \triangle \qquad \triangle$$

Where,

K = Membrane permeability

A = Area of the Membrane

H = Membrane thickness

T =△Osmotic pressure difference

P =△ Hydrostatic pressure difference.

These systems are generally appear in two different forms:

- The drug as a solid core together with electrolyte, which is dissolved by the incoming water. The electrolyte provides the high osmotic pressure difference.
- This system contains the drug in solution in an impermeable membrane within device. The electrolyte surrounds the bag.

Advantages:

i. This system can deliver large volumes and some are refillable.

ii. Release of drug is in theory independent of the drug's properties.

iii. Zero order release is obtainable.

Disadvantages:

i. Systems can be much more expensive than conventional counterparts.

ii. Quality control is more expensive than most conventional tablets.

2.3.5. Ion exchange systems:

This system generally uses resins composed of water insoluble cross linked polymers. These polymers contain salt forming functional groups in repeating positions on the polymer chain. The drug is bound to the resin and released by exchanging with appropriately changed ions in contacting with the ion exchange groups.

Resin +- drug-+x ---------→ Resin+- X-- + drug –

Resin +- drug-+Y ---------→ Resin+- Y-- + drug +

Where X- and Y+ are ions in the GI tract. The free drug then diffuses out of the resin. The drug resin complex is prepared either by repeated exposure of the resin to the drug in a chromatography column, or by prolonged contact in solution.

The rate of drug diffusing out of the resin is controlled by the area of diffusion, diffusion path length and rigidity of the resin, which is a function of the amount of cross-linking agent used to prepare the resin.

The system is advantageous for drugs that are highly susceptible to degradation by enzymatic process, since it offers a protective mechanism by temporarily altering the substrate. The limitation of this system is to release rate which is proportional to the concentration of the ions present in the area of administration.

2.4Drug properties relevant to controlled release formulation :

The design of controlled –release delivery system is subject to several variables of considerable importance. Among these are the route of drug delivery, the type of delivery system, the disease being treated, the patient, the length of therapy and the properties of the drug. Each of these variables are interrelated and this imposes certain constrains upon choices for the route of delivery, the design of the delivery system and the length of therapy. Properties of drugs are very important for designing a sustained release dosage form mainly physicochemical and biological properties of the drug are most important.

2.5Metoclopramide and ExtrapyramidalSymptoms:

Metoclopramide is a usefulmedication in the anesthesia provider'sarmamentarium. Its primary indication in the preoperativephase is to reduce gastric contents and increase lower esophagealsphincter tone for pharmacologic pulmonary aspiration prophylaxis. Metoclopramide can precipitate extrapyramidal symptoms(EPS)/drug-inducedmovement disorders (DIMD). Tardive dyskinesia and Parkinsonism generally seen after long-termuse,whereasdystonia and akathisia can occur after a single dose of metoclo-pramide. Recognition of dystonia and/or akathisia by the peri-anesthesia nurse after the administration of metoclopramide isimportant for prompt treatment of this distressing condition. It isimperative that the perianesthesia nurse is knowledgeable in metoclopramide's basic pharmacology, uses as an anesthetic adjunct,guidelines for administration, and EPS/DIMD associated reactions,as well asmeasuresthatmay reduce the incidence and/or facilitatetreatment of this medication-induced condition. This case reportpresents a male patient in his 40s experiencing akathisia after asingle

10-mg dose of metoclopramide.Keywords: metoclopramide, extrapyramidal symptoms, drug induced movement disorders, akathisia, case study, perianesthesiacare.

METOCLOPRAMIDE is a useful medicationin the anesthesia provider's armamentarium.It is administered in the preoperative phaseto reduce gastric contents and increase loweresophageal sphincter tone for pharmacologicpulmonary aspiration prophylaxis. Metoclopramide can result in extrapyramidal symptoms (EPS)/drug-induced movement disorder(DIMD) when administered during the perianesthesia/perioperative period.

LITERATURE REVEIW

ShalinModi*et al*(2011)[10]:Now a days as very few drugs are coming out of research and development and already existing drugs are suffering the problem of resistance due to their irrational use specifically in case of drugs like antibiotics. Hence, change in the operation is a suitable and optimized way to make the some drug more effective by slight alteration in the drug delivery.Sustained Release is also providing promising way to decrease the side effect of drug by preventing the fluctuation of the therapeutic concentration of the drug in the body. This article contains the basic information regarding sustained-release formulationand also the different types of the same**.**

Ramdas*et al* (2011)[11]: Oral sustained release dosage forms are the most commonly formulated but still offer highest attention in the area of novel drug delivery systems. (1-2). This system can also help in optimizing oral controlled delivery of drugs having 'absorption window' by continuously releasing drug prior to absorption window, for prolonged period of time thus causing optimal bioavailability (3). Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control the emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage forms (4). Prolonged gastric residence time (GRT) and controlled release of drugs within the GI tract helps to reduce dosing frequency and total dose, improve patient compliance and convenience, maintain a less fluctuating plasma level, as well as reduce GI side effects. Prolonging the GRT of therapeutic agents is thought to be beneficial especially under several circumstances such as for drugs acting topically on the gastric region, for drugs with a narrow therapeutic window or for drugs with the major absorption site in the upper GI tract (5-6).

S.A. Modi*et al* (2011)[12]:The objective of the present study is to prepare sustained release drug delivery system based on thematrix tablet for the freely water soluble drug Metoclopramide hydrochloride in order to achieve greater patient compliance. The sustained release formulations were prepared by using natural polymers like Dextrin, Guar gum and Xanthan gum. The formulations, with individual polymers were prepared in Drug: polymer ratio varying from 1:1:1 to 1:2:2 in the form of matrix tablet using wet granulation method. The formulations were subjected to *in-vitro* dissolution test studies for 10 hour. *In-vitro dissolution* studies were carried out in pH 1.2 and pH 6.8.Among all the formulations, the formulation F10 and F12, which

contained Drug: Guar gum: Xanthan gum in the ratio 1:2:1 and 1:2:2 respectively, showed desire drug release rate up to 10 hour.

Indranil Kumar Yadav*et al* (2010)[13]:The objective of the present study was to develop the oral sustained release matrix tablets of aceclofenac using hydrophilic and hydrophobic polymers. Aceclofenac is a non steroidal anti-inflammatory agent used in symptomatic treatment of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis and its biological half life is 4 hrs. FTIR studies were carried to know the interaction between the drug and polymer. Controlled release formulations of aceclofenac (200 mg) were prepared by direct compression method. The tablets were subjected to physicochemical, invitro drug release and stability studies. Optimization of the formulation was done by studying effect of drug to polymer ratio on drug release. FTIR studies indicated absence of any interaction between aceclofenac and polymers. The physicochemical properties of tablets were found within the limits. The drug release from optimized formulations F1, F4 and F7 was extended for a period of 12 hrs. The kinetic treatment to optimized formulations showed that the release of drug follows zero order model and Super Case II transport for F1 and F7 while the drug release of F4 was best explained by Higuchi's model and Super Case II transport. Release of the drug was retarded with increase in polymer concentrations. The optimized formulations were subjected to stability studies for three months at 45° temperature with RH 75±5%, and showed stability with respect to physicochemicalparameters and release pattern. Results of the present study indicated the suitability of hydrophilic and hydrophobic polymers in the preparation of matrix based sustained release formulation of aceclofenac.

R.Charulatha*et al* (2012)[14]:Carbamazepine is a widely used anti-epileptic drug in the therapy of psychomotor seizuresand trigeminal neuralgia. The objective of the present study is to prepare oral controlled release matrix tablet of carbamazepine (420 mg) by wet granulation technique using hydrophilic polymers such as HPMC, Sodium CMC of various concentrations. Its solubility was increased by making a complex with β –cyclodextrin thereby increasing its bioavailability. Eudragit incorporated as a release modifier due to its solubility in acidic medium. The tablets were evaluated for preformulation studies like angle of repose, bulk density, compressibility index and physical characteristics like hardness, weight variation, friability and drug content. *In-vitro* release of drug was performed in 0.1 N HCl for 2 hours PBS pH6.8 for 12

hours. All the physical characters of the fabricated tablet were within acceptable limits. *In vitro* release profile of marketed controlled release formulation (tegretol) showed the drug release 84% in 12th hour,where as our selected formulations F13 (HPMCK4m) released at 88% of drug in 12th hour respectively. The relative bioavailability of the selected formulation was 0.435 µg/ml of tmax at 12 hr compared with marketed product of 0.369µg/ml. The stability studies showed that it followed zero order kinetics when fitted to kinetic models (Higuchi, Hixson and Peppas).It was clear from the dissolution profile of carbamazepine from matrix tablets prepared using different polymers were indicated an increase in the polymer ratio retarded the drug release to a greater extent. As a concluding remark, F13 carbamazepine matrix tablet showed better oral bioavailability than the marketed tablet, and further animal studies/human studies could be under taken with large number of subjects in order to confirm these results.

V.C. Modi*et al* (2010)[15]:Sustained releases tablets of Diltiazem hydrochloride were formulated by employing hydroxypropyl methylcellulose (HPMC K100 M) and the sustained release behaviour of the fabricated tablets was investigated. Sustained release matrix tablets containing 120 mg Diltiazem hydrochloride were developed using different drug: polymer (HPMC K100 M) ratios. Tablets were prepared by wet granulation technique. Formulation was optimized on the basis of acceptable tablet properties and *invitro* drug release. The resulting formulation produced robust tablets with optimum hardness, consistent weight uniformity and low friability. All tablets but one exhibited gradual and near-complete sustained release for Diltiazem hydrochloride (96-100%) at the end of 24 h. The results of dissolutionstudies indicated that formulation B5 (drug to polymer 1:1.25) was found to be most successful as it exhibits drug release pattern very close to theoretical release profile. A decrease in release kinetics of the drug was observed on increasing polymer ratio.

Kamlesh J. Wadher*et al* (2011)[16]:Metformin hydrochloride is recommended globally as first line therapy due to its favorable profile on morbidity and mortality associated with type-2 diabetes mellitus. However, limitations of multiple dosing and risk of triggering gastrointestinal symptoms make its dose optimization difficult. Extended-release metformin matrix tablets were prepared by direct compression of drug and different pH-dependent (Eudragit L-100 and S-100) and pH-independent (Eudragit RLPO and RSPO) polymer combinations. The influence of varying the polymer/polymer (w/w) ratio was evaluated. Among the different examined polymer

blends, matrix tablets based on S-100/RLPO and S-100/RSPO mixtures gave the more sustained release pattern. The excipients used in this study did not alter physicochemical properties of the drug, as tested by Fourier transform Infrared Spectroscopy and the thermal analysis using differential scanning calorimetry. All the batches were evaluated for thickness, weight variation, hardness, and drug content uniformity. The *in vitro* drug dissolution study was carried out using USP 22 apparatus II, paddle method and the release mechanisms were explored. Mean dissolution time is used to characterize drug release rate from a dosage form and indicates the drug release retarding efficiency of polymer. Kinetic modeling of *in vitro* dissolution profiles revealed the drug release mechanism ranges from diffusion controlled to anomalous type. Fitting the data to Korsmeyer equation indicated that diffusion along with erosion could be the mechanism of drug release.

R. Gendle*et al* **(2010)**[17]: The objective of this work was to develop sustained release tablets of highly water soluble Tramadol HClusing polymers (HPMC K100M, HPMC K15M, HPMC K 4M) as cost effective, non toxic easily available and suitablehydrophilic matrix system. Sustained release tablet of Tramadol HCl (dose 50mg) were produced by wet granulationmethod. After the evaluation of physical characteristics of tablets. The dissolution test was performed in 0.1 N HCl fortwo hr. and phosphate buffer pH 6.8 for ten hr. The release profile remains unchanged after three months storage oftablets. The best fit release kinetics was achieved with the zero order plot followed by the Higuchi and Korsmyer andPeppas equation. The data obtained proved that the formulations are useful for a sustained release of Tramadol HCl dueto the percentage released after 12 hr. is nearly to 100%.

Suresh V Kulkarni43 *et al.*, (2010)[20]**:**investigation an attempt was made to reduce thefrequencyof dose administration and to improve the patient compliance by developingcontrolled release (CR) matrix tablet of Stavudine using naturally occurring (Guar gum and Xanthun gums) and Synthetic Polymers(HPMC and Ethylcellulose). Six batches of CRmatrix tablets of Stavudine were developed by usingwet granulation technique. Tablets were evaluated for weight variation, hardness,friability and *In vitro* dissolution studies. All formulation showed compliance withpharmacopoieal standards. Among the six formulations, F3 showed controlled release of drug for 12 hours with 91.65% drug release. The release data was fitted to various mathematical models such as, Higuchi, Korsmeyer-Peppas, First-order, and

Zeroorder to evaluate the kinetics and mechanism of the drug release was found to bediffusion coupled with erosion.

RaghavendraRao N.*et al.*, (2009)[21]:was to develop sustained release matrix tablets of water soluble Tramadol hydrochloride using different polymers viz.Hydroxy propyl methyl cellulose (HPMC) and natural gums like Karaya gum (KG)and Carrageenan (CG). Varying ratios of drug and polymer like 1:1 and 1:2 wereselected for the study. After fixing the ratio of drug and polymer for control therelease of drug up to desired time, the release rates were modulated by combinationof two different rates controlling material and triple mixture of three different ratecontrolling material. After evaluation of physical properties of tablet, the *in vitro* release study was performed in 0.1N HCl pH 1.2 for 2 hrs and in phosphate buffer pH 6.8 up to 12 hrs. The effect of polymer concentration and polymer blendconcentration were studied. Different ratios like 80:20, 60:40, 50:50, 40:60 and 20:80were taken. Dissolution data was analyzed by Korsmeyer-Peppas power lawexpression and modified power law expression. It was observed that matrix tabletscontained polymer blend of HPMC/CG were successfully sustained the release ofdrug upto 12 hrs. Among all the formulations, formulation F16 which contains 20%HPMC K15M and 80% of CG release the drug which follow Zero order kinetics via, swelling, diffusion and erosion and the release profile of formulation F16 was comparable with the marketed product. Stability studies (40±2ºC/75±5%RH) for 3months indicated that Tramadol hydrochloride was stable in the matrix tablets. TheDSC and FTIR study revealed that there was no chemical interaction between drugand excipients.

Jolly M. Sankalia49 *et al.*, (2008)[22]:examined in vitro–in vivo correlation for glipizidehydrophilic sustained-release matrices tablets on various polymers like ethyl cellulose, microcrystalline cellulose, hydroxyl propyl methylcellulose, xanthan gum,guar gum, Starch 1500, and lactose on in vitro release profiles was studied and fittedto various release kinetics models.

Alok Ray*et al* (2003)[23]:studied the role of modulating factors such as drug topolymer ratio, drug loading, particle size, and compaction pressure ant amount oflubricant on release Caffeine from tamarind seed polysaccharide, which is forhydrophilic matrix for drug delivery system. The

following observation on releaserate were made using Korsmeyer–Peppas's and Higuchi's equations I) thecompaction pressure had no significant effect on release. ii) the effect of particle sizepolysaccharide on release was insignificant except in the range of 250-150 microns.iii) the increase in polymer content showed decreases in both rate of release anddissolution. Iv) the increase in drug loading showed the rate of release anddissolution decreased. v) the presence of lubricant up to 2% had no effect on the rateof release. The mechanism of release was found to be anomalous (n>0.5) in all thecases.

Jordan*et al*[25] "Metoclopramide HCl showed controlled release behavior when embedded in a hydrophilic matrix of chitosan and sodium alginate. The in vitro release data was found to be first order according to the Higuchi mechanism. An in vivo evaluation of the metoclopramide controlled release matrix on six male volunteers was carried out. The plasma samples were analyzed using a high-performance liquid chromatography (HPLC) method using a mobile phase of acetonitrile:acetic acid (30:70), with the pH adjusted to 4.7, a reverse phase Hypersil BDS Phenyl column (4 μm, 250×4 mm) and the detection was performed at 305 nm. The controlled release formula was found to be effective in delaying absorption (t_{max} 4.5 h as compared to 1.2 h), reducing the peak plasma concentrations (C_{max} 63.4 ng/ml as compared to 95.9 ng/ml) and maintaining higher concentrations during the elimination phase when compared to the immediate release formula. This proves the suitability of the suggested system for further studies."

Monica R P Rao *et al*[26] "Metoclopramide HCl is mainly used as an anti-emetic agent in the cancer chemotherapy. It alsostimulates the upper GI tract and is used in the management of some forms of nausea, vomiting and pain associated withmigraine as well as in gastric stasis where quick onset of action is required. Conventional tablet may give delayed onset of action (probably 1.5-2 hrs) which may be over come by administering immediate release tablets. The development of immediate release tablet formulations is based on the use of super disintegrantsseparately or in combination. Seven formulations were prepared using simplex centroid mixture design where sodium starch glycolate (X1), cross carmellosesodium (X2) and pregelatinised starch (X3) were selected as independent variables and dependent variables were

disintegration time (Y1) and release at 15 minutes (Y2). Response surface plots were drawn, and optimum formulations were selected by grid search method. X1, X2 and X3 when used individually gave satisfactory results but when used in combination gave better results. The results showed a good relationship between the experimental and predicted values, which confirms the predictability of the model."

R F Thoeni et ai[27] **"**The value of orally administered metoclopramide hydrochloride to enhance bowel opacification during abdominal and pelvic computed tomography (CT) was analyzed prospectively in 202 patients in a control group and 334 patients in an experimental group who received 10 mg of metoclopramide with the first dose of oral contrast material. Five hundred milliliters of 2% sodium diatrizoate was given orally 45-60 minutes and 30 minutes before the study, and 250 mL was given 5-10 minutes before the study. Opacification of stomach, duodenum, and small and large bowels was graded from 0 to 3+, and the presence of pseudotumors or side effects from metoclopramide were noted. No significant difference was found in the opacification of stomach, duodenum, and jejunum between control and experimental studies. Opacification was significantly better in metoclopramide studies than control studies in the proximal ileum (P less than .05), distal ileum (P less than .05), right colon (P less than .05), and transverse colon (P less than .05). Pseudotumors were seen in 7% of control and 3% of experimental subjects. No side effects were encountered. Routine oral administration of metoclopramide before abdominal and pelvic CT examinations is recommended for rapid opacification of the ileum and proximal colon for all outpatients and for inpatients who must undergo CT on an emergency basis."

V. F. Patel *et al* (2007)[24]studied the influence of viscosity of hydroxypropyl methyl cellulose and types of filler on Dipyridamole release from floating matrix tablet using 3 full factorial design. Multiple regression analysis was performed for the dependant variables. To evaluate contribution of the factors with their levels two way ANOVA was performed followed by Tukey test. Polynomial equations and response surface plots were generated for all dependant variables. It was observed that both the factors had significant influence on all dependant variable studied.

It was observed as the viscosity of polymer increases the release rate constant was decreased. Release rate obtained was highest when microcrystalline cellulose was employed as filler followed by dicalcium phosphate and lactose. Mechanism of release was anomalous type and depends upon viscosity of polymer and types of filler used. A major controlling factor for kinetics of drug release was viscosity of polymer and it can be modified by incorporation of different types of filler.

Santanu Ghosh41 *et al.*, (2010)[18]: was to develop matrix tablets for oral controlledrelease of aceclofenac. Matrix tablets of aceclofenac, using various viscosity of hydrophilic polymer HPMC in two different proportions, hydrophobic polymer ethylcellulose and Guar gum were prepared by wet granulation method and subjected to*in vitro* drug release studies. Based on the results of the *in vitro* studies, it wasconcluded that the HPMC matrix tablets provided oral controlled release ofaceclofenac.

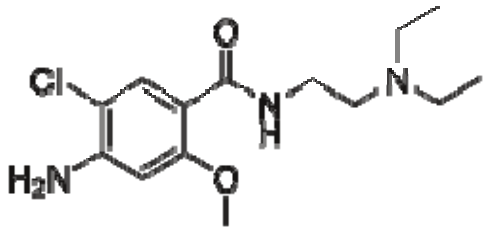
SantanuGhosh and Barik42 *et al.*, (2010)[19]: was to develop matrix tablets for oral controlled release of aceclofenac using ethyl cellulose, guar gum, and various gradesof cellulose polymers.The release profile of one of the formulated aceclofenactablets, which containedhydroxypropyl methyl cellulose, was statistically similar tothat of the commercial aceclofenac brand in all the dissolution media. The resultindicate that it is feasible to achieve a stable once daily sustained release aceclofenactablet formulation by using HPMC k4M of 4000cps viscosity grade as matrixmaterial.

DRUG AND EXCIPIENT PROFILE

DRUG PROFILE

Metoclopramide[28,29]

- Chemical name : 4-amino-5-chloro-N-(2-(diethylamino)ethyl)-2-methoxybenzamide
- Chemical structure



- Molecular weight :- 299.80 g/mol
- Melting point :- 147.3 °C (297 °F)
- Half Life :- 5–6 hours
- Drug category [30]:- antiemetic and gastroprokinetic agent
- Metoclopramide is commonly used to treat nausea and vomiting (emesis) associated with conditions including: emetogenic drugs, uremia, radiation sickness, malignancy, labor, and infection.[6][7] It is also used by itself or in combination with paracetamol (acetaminophen) (paracetamol/metoclopramide available in the UK as Paramax, and Australia as Metomax) or aspirin (MigraMax) for the relief of migraine.
- Mode of Action[31,32]

- ✓ Metoclopramide was first described by Dr. Louis Justin-Besançon and C. Laville in 1964.[2] It appears to bind to dopamine D_2 receptors where it is a receptor antagonist, and is also a mixed 5-HT_3 receptor antagonist/5-HT_4 receptor agonist.
- ✓ The anti-emetic action of metoclopramide is due to its antagonist activity at D_2 receptors in the chemoreceptor trigger zone (CTZ) in the central nervous system (CNS)—this action prevents nausea and vomiting triggered by most stimuli.[3] At higher doses, 5-HT_3 antagonist activity may also contribute to the anti-emetic effect.

- ✓ The prokinetic activity of metoclopramide is mediated by muscarinic activity, D_2 receptor antagonist activity and 5-HT_4 receptor agonist activity.[4][5] The prokinetic effect itself may also contribute to the anti-emetic effect.

Adverse Effect[33,34,35]*:*

- ➢ Common adverse drug reactions (ADRs) associated with metoclopramide therapy include: restlessness, drowsiness, dizziness, lassitude, and/or dystonia. Infrequent ADRs include: headache, extrapyramidal effects such as oculogyric crisis, hypertension, hypotension, hyperprolactinaemia leading to galactorrhoea, constipation, and/or depression. Rare but serious ADRs associated with metoclopramide therapy include: agranulocytosis, supraventricular tachycardia, hyperaldosteronism, neuroleptic malignant syndrome, akathisia and/or tardive dyskinesia.[7] Dystonic reactions are usually treated with benztropine or procyclidine.
- ➢ The risk of extrapyramidal effects is increased in young adults (<20 years) and children, and with high-dose or prolonged therapy.[6][7] Tardive dyskinesias may be persistent and irreversible in some patients.
- ➢ In 2009, the U.S. Food and Drug Administration required all manufacturers of metoclopramide to issue a black box warning regarding the risk of tardive dyskinesia with chronic or high-dose use of the drug.[11]

EXCIPIENT PROFILE

1.MICROCRYSTALLINE CELLULOSE[36]:

- Synonym:Cellulose gel, crystalline cellulose, Avicel PH 101, 102
- Empirical Formula: $(C_6H_{10}O_5)_n$
- Molecular weight:Approx.36000
- Description: Purified, partially depolymerised cellulose occurs as a white, odorless, tasteless, crystalline, powder composed of porous particles available in different particle size grades with different properties , i.e. 101 ,102
- Bulk Density: 0.28gm/cm ^{3}
- Tapped Density: 0.43gm/cm^3
- Solubility: Insoluble in water, dilute acids and most organic solvents .Slightly soluble in sodium hydroxide solution.
- Stability and storage condition: Stable and hygroscopic. Store in a well – closed container.
- Incompatibility: None cited in the literature.
- Handling precautions: No restrictions.
- Uses: Tablet binder / diluent (5-20%), tablet disintegrant (5-15%), tablet glidant (5-15%) antiadherent (5-20%), capsule diluents (10-30%).

2.MANNITOL[37]

- Chemical name:hexanitromannitol
- Synonym: mannitolhexanitrate, nitromannite, nitromannitol, nitranitol, mannitrin
- IUPAC: (2R,3R,4R,5R)-Hexane-1,2,3,4,5,6-hexol-1,2,3,4,5,6-hexanitrate
- Molecular formula: $C_6H_8N_6O_{18}$
- Molar mass: 452.15712
- Density: 1.604 g/cc
- Melting point: 112 °C = 234 °F

- Formula:$C_6H_{14}O_6$
- Mol. mass:182.172
- Use: This polyol is used as an osmotic diuretic agent and a weak renalvasodilatorMannitol is also the first drug of choice for the treatment of acute glaucoma in veterinary medicine. It is administered as a 20% solution IV. It dehydrates the vitreous humor and, thus, lowers the intraocular pressure. However, it requires an intact blood-ocular barrier to work. Mannitol can also be used to temporarily encapsulate a sharp object (such as a helix on a lead for an artificial pacemaker) while it is passed through the venous system. Because the mannitol dissolves readily in blood, the sharp point will become exposed at its destination.Mannitol may be administered in cases of severe Ciguatera poisoning. Severe ciguatoxin, or "tropical fish poisoning" can produce stroke-like symptoms. Mannitol is the primary ingredient of Mannitol Salt Agar, a bacterial growth medium, and is used in others. In oral doses larger than 20 g, mannitol acts as an osmotic laxative, and is sometimes sold as a laxative for children

3.HYDROXY PROPYL METHYL CELLULOSE[38]

- Synonym: Benecel MHPC; E464; hydroxypropyl methylcellulose; HPMC;hypromellosum; Methocel; methylcellulose propylene glycol ether; methyl hydroxypropylcellulose; Metolose; MHPC; Pharmacoat; Tylopur; Tylose MO.
- Nonproprietary Name: BP: Hypromellose JP: HypromellosePhEur: Hypromellose USP: Hypromellose
- Empirical Formula: $CH_2CH(OH)CH_3$.
- Molecular Weight: 591.3
- Description: Fine, white, precipitated or milled, impalpable powder of low bulk density. Odour and taste are slight but characteristic. The powder is readily adheres to the skin.
- Density, bulk: 0.519 gm/cm^3
- Density, tapped: 0.286gm/cm^3
- Melting point: 117-150^{0}C

- Stability And Storage Condition : Stable, non self polymerisable, store in cool and dry place in a well closed container.
- Incompatibilities: Incompatable with strong acid substances, alkaline substances, iron salts, avoid mixing with strong oxidizing materials .Use with caution with drugs , which are incompatible with alkali.
- Uses: POLYMERt, glidant or antiadherent (0.25-2.0%).

4.MAGNESIUM STEARATE[39]

- Synonym: Metallic stearate; octadecanoic acid; magnesium salt; Stearic acid.
- Nonproprietary Name: Magnesium Stearate (BP); Magnesium Stearate (JP); Magnesium Stearate(USP).
- Empirical Formula: $C_{36}H_{70}MgO_4$
- Molecular Weight: 591.3
- Description: Fine, white, precipitated or milled, impalpable powder of low bulk density. Odour and taste are slight but characteristic. The powder is readily adheres to the skin.
- Density, bulk: 0.519 gm/cm^3
- Density,tapped: 0.286gm/cm^3
- Melting point: 117-150^{0}C
- Stability And Storage Condition : Stable, non self polymerisable, store in cool and dry place in a well closed container.
- Incompatibilities: Incompatable with strong acid substances, alkaline substances, iron salts, avoid mixing with strong oxidizing materials .Use with caution with drugs , which are incompatible with alkali.
- Uses: tablet and capsule lubricant, glidant or antiadherent (0.25-2.0%).

5.Carboxymethylcellulose Sodium[40]

- Nonproprietary Names: Carmellose Sodium
- Synonyms: Akucell, Aqualon CMC, Aquasorb, Blanose, Carbose D, carmello- sum natricum, Cel-O-Brandt,cellulose gum, Cethylose, CMCsodium, E466; Finnfix,

Glykocellan, Nymcel ZSB; SCMC; sodium carboxymethylcellulose; sodium cellulose glycolate; Sunrose; Tylose CB; Tylose MGA; Walocel C; Xylo-Mucine.

- Chemical Name and CAS Registry Number :Cellulose, carboxymethyl ether, sodium salt
- Functional Category: Coating agent; stabilizing agent; suspending agent; tablet andcapsule disintegrant; tablet binder; viscosity-increasing agent; water-absorbing agent.
- Applications in Pharmaceutical Formulation :Carboxymethylcellulose sodium is widely used in oral and topicalpharmaceutical formulations, primarily for its viscosity-increasing properties. Viscous aqueous solutions are used to suspend powders intended for either topical application or oral and parenteral administration.Carboxymethylcellulose sodium may also beused as a tablet binder and disintegrant, (3–6)and to stabilizeemulsions. (7,8) Higher concentrations, usually 3–6%, of the medium viscositygrade are used to produce gels that can be used as the base forapplications and pastes; glycols are often included in such gels to
- Density (bulk): 0.52 g/cm3
- Density (tapped): 0.78 g/cm3
- Dissociation constant pKa : 4.30
- Melting point: Browns at approximately 2278C, and chars at approximately 2528C.
- Moisture content :Typically contains less than 10% water.However, carboxymethylcellulose sodium is hygroscopic and absorbs significant amounts of water at temperatures up to 378C at relative humidities of about 80%.
- Solubility :Practically insoluble in acetone, ethanol (95%), ether, and toluene. Easily dispersed in water at all temperatures, forming clear, colloidal solutions. The aqueous solubility varieswith the degree of substitution (DS).Viscosity Various grades of carboxymethylcellulose sodium are commercially available that have differing aqueous viscosities, Aqueous 1% w/v solutions with viscosities of 5–2000mPa s (5–2000 cP) may be obtained. An increase in concentration results in an increase in aqueous solution viscosity.
- Stability and Storage Conditions:Carboxymethylcellulose sodium is a stable, though hygroscopicmaterial. Under high-humidity condtions, carboxymethylcellulose sodium can absorb a large quantity (>50%) of water. In tablets, this has been associated with a decrease in tablet hardness and an increase in disintegration time.

- Incompatibilities: Carboxymethylcellulose sodium is incompatible with strongly acidic solutions and with the soluble salts of iron and some other metals, such as aluminum, mercury, and zinc. It is also incompatible with xanthan gum. Precipitation may occur at pH < 2, and also when it is mixed with ethanol (95%). Carboxymethylcellulose sodium forms complex coacervates with gelatin and pectin. It also forms a complex with collagen.

AIM AND OBJECTIVES

- The aim of the present study was to develop the oral sustained release matrix tablets of Metoclopramide using hydrophobic polymers.
- These dosage forms are designed to deliver the drug at a controlled and predetermined rate, thus maintaining a therapeutically effective concentration of the drug in the systemic circulation for a long period of time.
- To increase duration of action.
- To achieve better patient compliance.
- To maintain steady state concentration of drug in plasma.
- To reduce dosing frequency.
- Cost effective.

PLAN OF WORK

- Literature survey.
- Procurement of drug and polymer substances.
- Preformulation studies.
- Preparation of Std. Curves of Metoclopramide HCL
- Formulation development of SR tablet.
- Evaluation of SR tablet for
- Extended evaluation & optimize batch (drug release kinetic std.)
- Stability studies of the optimized batch.

MATERIALS AND METHODS

Table -1Materials and manufacturer

Sr.No.	Materials	Monograph	Manufactures
1.	Metochlopramide Hydrochloride	IP/BP/USP	Mission Vivacare Limited
2.	Microcrystalline cellulose	IP	Reliance cellulose (P) Ltd.
3.	Mannitol	IP	Signet Pharma
4.	Hydroxyl propyl methyl cellulose	IP	R A Chemicals
5.	Sodium carboxyl methyl cellulose	BP	FMC ,Ireland
6.	Magnesium stearate	IP	VasundharaRasayans ltd.

Table -2Equipments used in the formulation

Sr.No.	Instruments	Manufacturer
1	Electronic Balance	Shimadzu Corporation AW 220 and BX 6205
2	Tray Dryer	Erweka Pvt. Ltd.
3	Dissolution Apparatus (USP)	Electrolab Pvt. Ltd
4	High Performance Liquid Chromatography	Agilent Ltd. 1100
5	Tablet Hardness tester	Vankel Ltd. K200

6	Friability test apparatus	Electrolab Pvt. Ltd EF 2 USP
7	Ultra Violet Visible Spectrophotometer	Shimadzu Corporation UV-1700
8	FTIR Spectrometer	Shimadzu Corporation, 8400S
9	Tap density Apparatus	Erweka Pvt. Ltd
10	Granulate Flow Tester	Erweka Pvt. Ltd
11	Vernier Caliper	Digimatic
12	pH Meter,	Systronics(335)
13	LOD apparatus	Sartorius

PREFORMULATION

Preformulation is a branch of pharmaceutical sciences that utilizes biopharmaceutical principles in the determination of physiochemical properties of a drug substance. The goal of pre-formulation studies is to choose the correct form of the substance, evaluate its physical properties and understanding of the material's stability under various conditions, leading to the optimal drug delivery system. The preformulation study focuses on the physiochemical parameters that could effect the development of efficacious dosage form. These properties may ultimately provide a rationale for formulation design. Also it will help in minimizing the problems in later stages of drug development, reducing drug development costs decreasing products time to market. It gives the information needed to define the nature of the drug substance and provide framework for the drug combination with pharmaceutical excipients in the dosage form.

Objective:

The overall objective of preformulation testing is to generate information useful to the formulation in developing stable and bioavilable dosage form.

Preformulation encompasses at least following test**.**

I) Bulk Characterization:

- Crystalline And Polymorphism, hygroscopicity.
- Powder properties (flow, compaction, density, particle size, surface area etc.)
- Microscopy (morophology, particle characteristics)
- Molecular spectroscopy (FT-IR)

II) Solubility Analysis:

- Ionization constant (pka)
- PH solubility profile
- Common ion effect
- Thermal effect on solubility
- Solubilization
- Partition coefficient (logP or logD)
- Dissolution

III) Stability Analysis:

- Stability (heat, light, base, acid, oxidizer)
- Solution stability
- Solid-state stability
- Excipient compatibility

Identification of drug

The identification of drug was done by IR Spectroscopy.

Method: Triturate 1-2 mg of the substance to be examined with 300-400 mg, unless otherwise specified, of finely powdered and dried potassium bromide R or potassium chloride R. These quantities are usually sufficient to give a disc of 10-15 mm diameter and a spectrum of suitable intensity. Infrared spectrometers are used for recording spectra in the region of 4000-650

Preformulation stability studies are usually the first quantitative assessment of chemical stability of a drug as well as stability in presence of other excipients. The primary objectives of this investigation are

identification of stable storage conditions for drug in the solid state and identification of compatible excipients for a formulation.

For drug excipients compatibility study selected excipients given below:-

Table -3 Drug –excipients compatibility study:

Sr.no.	Excipients	Properties
1.	Microcrystalline cellulose	Diluents
2.	Mannitol	Diluents
3.	Hydroxyl methyl propyl cellulose	Polymer
4.	Sodium Carboxyl methyl cellulose	Polymer
5.	Magnesium stearate	Glidant

According to the functional category these excipients were mixed in the different ratio. These mixtures were kept at 30^0C +65% RH, and 40^0C+75%, in a 2ml glass vial in exposed condition for 1 month.

At interval of 4 weeks, the sample was withdrawn and subjected for analysis and related substances. At the interval of 2 week, the samples were withdrawn and given to analytical development for analysis of following parameters:

- Moisture content
- Assay
- Related Substances

Table .4 PHYSICAL OBSERVATION OF COMPATIBILITY STUDY:

Drug & Excipients (Ratio 1:1)	Observation			Result
	Initial	30^0 C/65% RH after 30 days	40^0 C/75% RH after 30 days	
Metoclopramide Hydrochloride	White to off white powder	White to off white powder	White to off white powder	Compatible
Metoclopramide Hcl + HPMC	White to off white powder	White to off white powder	White to off white powder	Compatible
Metoclopramide Hcl + Sodium CMC	White to off white powder	White to off white powder	White to off white powder	Compatible
Metoclopramide Hcl + Mannitol	White to off white powder	White to off white powder	White to off white powder	Compatible
Metoclopramide Hcl + Microcrystalline Cellulose	White to off white powder	White to off white powder	White to off white powder	Compatible
Metoclopramide Hcl + Mg Stearate	White to off yellow powder	White to off yellow powder	White to off yellow powder	White to off white powder

Based on results following excipients were used to fabricate robust formulation of Metoclopramide Hcl sustained release matrix tablets.

Table 5 Selected excipients for prototype formulation:

Sr. no.	Excipients	Category
1.	Microcrystalline cellulose	Diluents
2.	Mannitol	Diluents
3.	Hydroxyl methyl propyl cellulose	Polymer
4.	Sodium Carboxyl methyl cellulose	Polymer
5.	Magnesium stearate	Glidant

Evaluation of Metoclopramide Hcl sustained release matrix tablets

1) Angle of repose[41]: it was measured by fixed funnel. The fixed funnel method employ a funnel that was secured with its tips at a given height H, above graph paper that was placed on a flat horizontal surface. Granules were carefully poured through the funnel until the apex of the conical pile just touches the tips of the funnel. Thus, with R being the radius of the base of the conical pile.

$\tan \theta = H/R$

Where,

θ = angle of repose

H =Height of pile

R = Radius of pile

Table 6 Angle of Repose

ANGLE OF REPOSE	PROPERTIES
25-30	Excellent
31-35	Good
36-40	Fair
41-45	Passable
46-50	Poor
51-55	Very poor
>56	Extremely poor

2) Determination of tap density and bulk density[41]: An accuratelyweighed quantity of the powder (W), was carefully poured into the graduated cylinder and the volume (V_0) was measured. Then the graduated cylinder was closed with lid, set in to the density determination apparatus, (Erweka Pvt. Ltd). The density apparatus was set for 100 taps and after that the volume (V_f) was measured and continued operation till the two consecutive readings were equal. The bulk density, and tapped density were calculated using the following formulas,

Bulk density = W/V_o

Tapped density = W/ V_f

Where,

W = weight of powder

V_o = Initial volume

V_f = final volume

3) **Compressibility index (Carr index)[41]:**

Compressibility index is an important measure that can be obtained from the bulk and tapped densities.carrs index a material having values of less than 15 to 20 % is defined as the free flowing material.

$$Ci = \frac{(V_0 - V_f)}{V_o} \times 100$$

Table 7Compressibility index

%Compressibility index	Properties
5 – 12	Free flowing
12 – 16	Good
18 – 21	Fair
23 – 35	Poor
33 - 38	Very poor
>40	Extremely Poor

4)Hausner Ratio[41]: It indicates the flow properties of the powder and is measured by the ratio of tapped density to bulk density.

Hausner ratio =tapped density/ bulk density

Table 8Hausner ratio

Sr. No	Hausner ratio	Property
1	0-1.2	Free flowing
2	1.2-1.6	Cohesive powder

5) Sieve analysis: the main aim of sieve analysis is to determine the different size of particles present. A series of standard sieves were stacked one above the other so that sieves with larger pore size (less sieve number) occupy top position followed by sieves of decreasing pore size (larger sieve number) towards the bottom

Procedure: A series of sieves were arranged in the order of decreasing pore diameter. (Increasing in sieve number) i.e. sieve numbers #20, #40, #60, #100. 100gm of drugs were weighed accurately and transferred to sieve #20 which kept on top. The sieves were shaken for about 5 minutes. Then the drug retained on each sieve were taken, weighed separately and expressed in terms of percentage.

6) L.O.D. :(loss on drying) of granules- the main aim of LOD of granules is to find out the presence of moisture content.

Procedure: LOD of granules was determined by using I.R. moisture balance (Sartorius).Required amount of granules was placed on I.R. plate and temperature was maintained at 105^0 C for 5 minutes. (Limit of moisture contained was 1.6%).

EVALUATION OF TABLET:

Description: Uncoated oval shaped embossed tablets were prepared. Check a representative sample for the above description.

1) Tablet dimensions[41,43]: Thickness and diameter were measured using a calibrated dial caliper[s]. Ten tablets of each formulation were evaluated.

2) Hardness[43]**:** Monsanto hardness tester was used to evaluate hardness of tablet. The tester consists of a barrel containing a compressible spring held between two plungers. The lower plunger was placed in contact with the tablet, and a zero reading was taken. The upper plunger was then forced against a spring by turning a threaded bold until the tablet fractures. As the spring compressed, a pointer rides along a gauge in the barrel to indicate the force .The force of fractured recorded, and the zero force reading was deducted it. Ten tablet of each formulation were evaluated.

3) Friability[41,42,43]**:** weigh accurately 20 tablets and place them in the friability test apparatus. Adjust the timer to 4 minutes. Operate the apparatus at 25 ±1 rpm and observe the tablets while rotating .No tablet should be stick to the walls of apparatus. Take the tablet out and observe. No capping should be observed. Weigh the tablet, after dedusting excess powder from their surface.

Calculation: calculate the Friability in % using formula:-

$$\text{Friability} = \frac{(W_1 - W_2)}{W_1} \times 100$$

Where,

W_1= Initial weight of tablet taken,

W_2=final weight of tablet after testing.

4) Weight variation[44,47,48]**:** Twenty tablets were selected randomly. Tablets were weighed individually and average weight was calculated. Then deviation of each tablet from average weight was calculated and percent deviation was computed. Standard deviation was compared with the U.S.P. limit.

Table 9 U.S.P. weight variation limit of uncoated tablet:

Average weight of tablet	Percentage deviation
130 or less	10
130-324	7. 5
More than 324	5

5)Standard Calibration Curve For Metoclopramide Hcl :100mgmetoclopramide hydrochloridewas dissolve in 100ml of 0.1N Hcl. From the stock solution aliquots of 10, 20,30,40,50, 60, 70, 80, 90, 100ml were pipette out and made up to 100ml with 0.1N Hcl. The absorbance of above solution was measured at 306 nm by U.V. spectrophotometer. The standard graph was plotted.

6) **AssayFor Metoclopramide Hcl**[45,46] -Weigh and powder 20 tablets. Weigh accurately a quantity of the powder equivalent to 10 mg of anhydrous metoclopramide hydrochloride, add 50 ml of *0.1M hydrochloric acid*, heat on a water-bath at 70^{o} for 15 minutes, cool, dilute to 100.0 ml with water and filter. To 20.0 ml of this solution add 15 ml of 1.25M sodium hydroxide and extract with three quantities, each of 30 ml, of chloroform, dry each extract with anhydrous sodium sulphate and filter. Dilute the combined extracts to 100.0 ml with chloroform and mix. Measure the absorbance of the resulting solution at the maximum at about 305 nm

7) Stability study[49,50,51]**:**An ethical drug manufacturer is committed to provide to his consumers drug products, which are efficacious and safe. This can be ensured only by instituting a sound programme to study the stability of a product during its various phases of development and to arrive at the proper storage condition and the expiry period under those conditions. This is a requirement in most of the countries and is stipulated by the regulatory agencies of those countries. These studies would very quickly identify the need, if any, to stabilize the active substance or the formulation, and invaluable time and effort from being spend on marketable formulation. With the recent trend towards globalization of manufacturing operation, it is imperative that the final product be sufficiently rugged for marketing worldwide under various climatic conditions including tropical, subtropical temperature. Metoclopramide Hcl sustained release matrix tabletsformulated in the present study were subjected to accelerated stability studies. The stability studies of formulated tablets were carried out at 40^{0} C, RH 75% and at room temperature for one month. The effect of temperature and time on the physical characteristics of the tablet was evaluated for assessing the stability of the prepared formulations. The stability studies were carried out when the room temperature was 20^{0} to 25^{0} C. the different parameter that were studied are % drug content, and in vitro dissolution study.

IN-VITRO STUDY:

DISSOLUTION MEDIUM: 0.1 N HCL,900ml, Apparatus type –Basket Type ,

The formulations were subjected to in vitrodissolution study using USP dissolution apparatus. The percentage of drug release was calculated for different formulation at different time intervals.

EXPERIMENTAL

MANUFACTURING PROCESS

FORMULATION OF SUSTAINED RELEASE METOCLOPRAMIDE HYDROCHLORIDE MATRIX TABLETS:

Formulation of sustained release Metoclopramide hydrochloride matrix tablets was done by in two steps.

First step:-Components used for formulation of tablets were mixed properly by using turbula mixer for 15 minutes.

Second step: -In second step the above mixture was compressed by using tablet punch machine of 10mm flat punches

The tablets were prepared by using different concentration of the polymer and their suitable combinations.

Table -10:Details of design, findings, and summary of key developmental batches

Ingredients	F1	F2	F3	F4	F5	F6	F7
Metoclopramide HCl	30	30	30	30	30	30	30
HPMC	90	90	30	90	70	70	70
Sodium CMC	50	30	90	30	30	50	30
Mannitol	-	-	-	20	20	20	40
Microcrystalline Cellulose	30	50	50	30	50	30	30
Mg Stearate	2	2	2	2	2	2	2

- **All quantity in mg /tablet**
- **Compression weight of tablet -202 mg /tab**

Prototype formulation by direct compression method-

The direct compression of tablet performed into three steps

- **Dry Mixing-**

  MCC, Mannitol pass through Sieve no 30 and Sodium CMCand HPMC pass through sieve no 40 and mix.

- **Lubrication-**

  Metoclopramide Hcl, magnesium stearate was bag blended. Blend pass through 40 screens and then above dried granules were mixed with the blend in suitable blender.

- **Compression-**

  Lubricated granules compressed into tablet by using single rotatory tablet punching machine,16 stations. With D tooling 10mm round shape punch set.

RESULT AND DISCUSSION

Tablets with sustained drug delivery were prepared and evaluated with aim to obtain tablet to deliver the drug at a controlled and predetermined rate, thus maintaining a therapeutically effective concentration of the drug in the systemic circulation for a long period of time.

Prior to the formulation, preformulation study was carried out on drug and excipients, in the present work,formulation part divided in to two steps. In first step, all ingredients with MCP Hcl were mixed.

In second step the tablets were prepared by using different polymers and its different combination ratio were selected for formulation. The detailed composition is shown in table no10 the tablets were evaluated for various parameters such as thickness, hardness, friability, weight variation, drug content and in-vitro study.

PREFORMULATION STUDY:

To ensure the compatibility of drug with excipients the IR spectra for pure drug and prepared powder blend was obtained and analyzed for principle peaks.

The peaks obtained in powder blends of formulations were almost identical to those obtained for pure drug reveling that there was no interaction between drug and polymers used in formulations.

Standard curve of Metoclopramide Hcl:

Table shows the absorbance readings of Metoclopramide Hclbetween 10-100mcg/ml in 0.1N Hcl.

Evaluation of Blend:

Angle of repose:

The angles of repose of all formulated batches obtained are shown in table no 12. This implies fair free flowing nature of powder blends. These values were found to be satisfactory to give good flow of powder blends.

Hausner ratio:

The values of Hausner ratio obtained are shown in table no 12. indicating that the powder blends had good flow ability and compressibility.

Bulk Density And Tapped Density:

The values of bulk density and tapped density obtained are shown in tableno 12. indicating that the powder blends had good compressibility.

Evaluation of tablet

I) Tablet Dimensions:

Tablet dimension include thickness and diameter of tablet. Five tablet of each formulation were evaluated shown in table no 12.

II) Hardness:

Five tablet of each formulation were evaluated and mean hardness values are shown in table.no 12. The values reveals that the tablets are having good mechanical strength.

III)Friability:

Friability values of each formulation are recorded in tableno 12. . these values are within acceptable limit , implies good compactness and strength of each formulation. This also indicates that direct compression method is acceptable for technique for formulating rapidly disintegrating sublingual tablet.

IV) Weight Variation:

Twenty tablets of each formulation were evaluated .the mean values of each formulation are recorded in tableno 12. The values obtained indicate that all the tablet of different formulations falls within the U.S.P. specification.

The weight variation of all tablets was satisfactory due to good flow ability of powder blends .desired packaging characteristic and uniform dies fill of the formulations. This is supported by the acceptable flow properties of powder blend obtained.

V) Content uniformity of active ingredient:

The content uniformity was calculated on all the formulation of rapidly disintegrating sublingual tablets. The study was carried in triplicate. Tableno 12.shows the results of the drug content uniformity in each formulation with S.D.values.

These values are found satisfactory, which ensures dosage uniformity and meets with requirements of USP.

viii) In Vitro Drug Result :

Table - 11.Standardcalibration values of Metoclopramide Hcl

Sr. no.	CONC (mcg/ml)	ABS (nm)
1	10	0.0733
2	20	0.1432
3	30	0.2131
4	40	0.2782
5	50	0.3471
6	60	0.4190
7	70	0.4867
8	80	0.5525
9	90	0.6225
10	100	0.6950

Standard plot ofMetoclopramide Hcl:

Standard plot of Metoclopramide Hclwas plotted by taking absorbance on X axis and concentration in mcg/ml on Y axis. The plotted graph show below

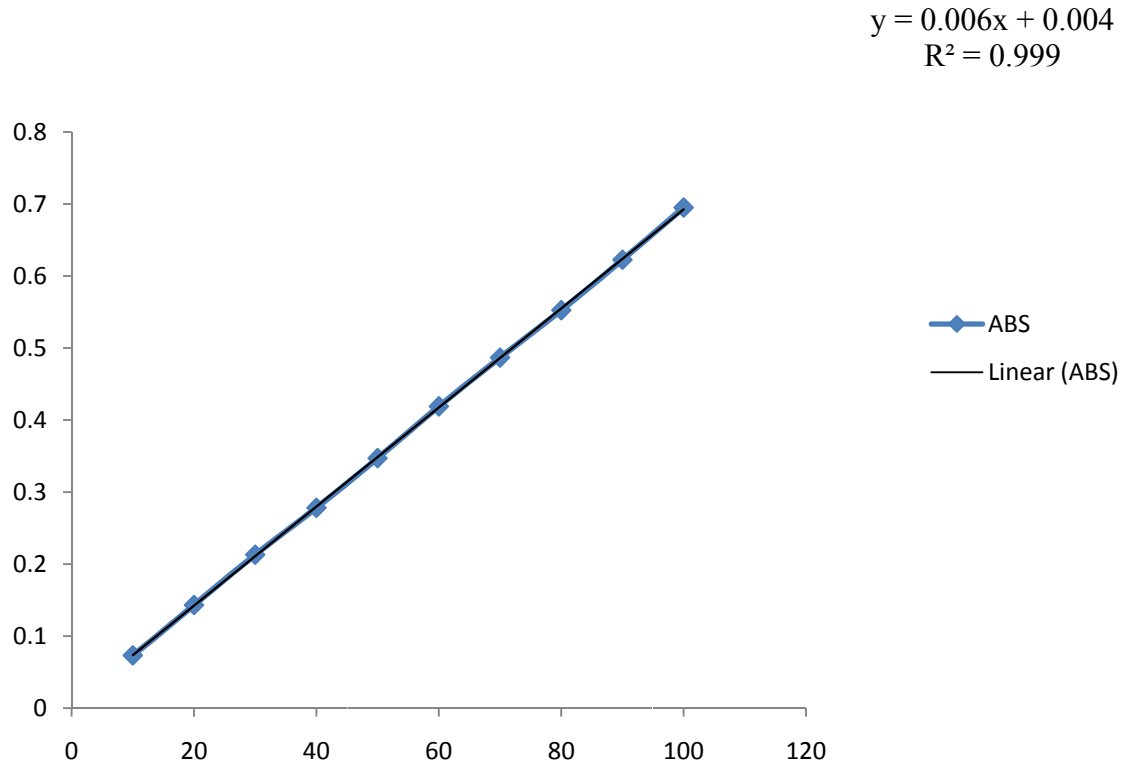


Fig .7 Standard curve of Metoclopramide Hydrochloride

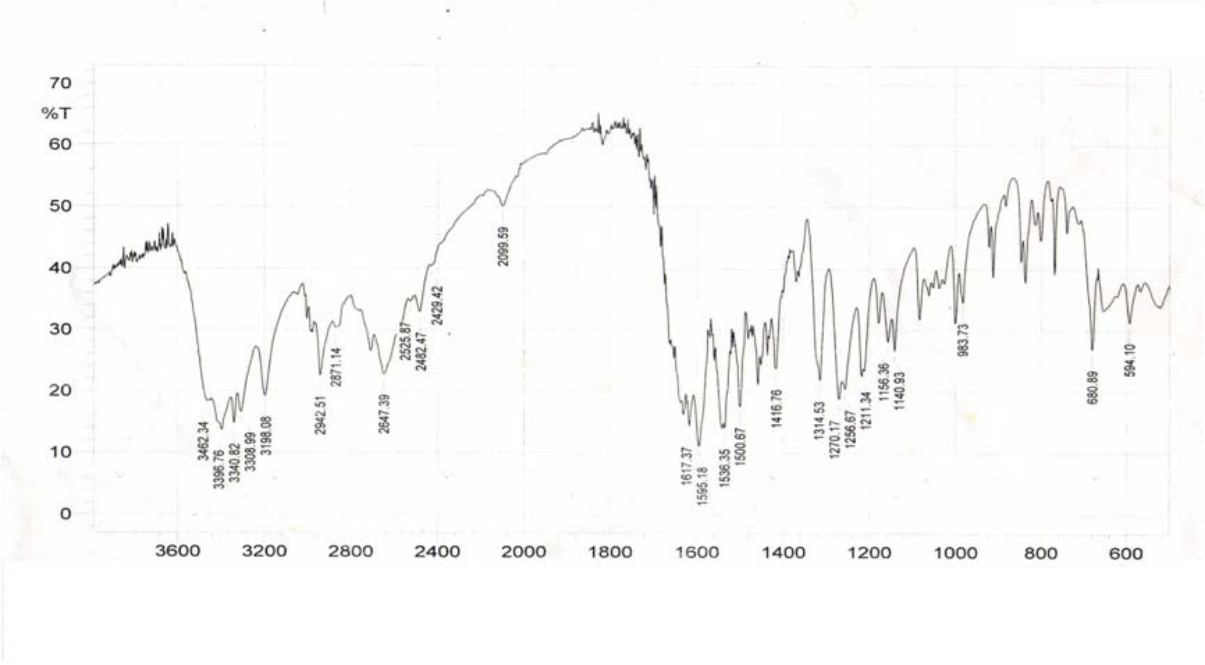


Fig 8 I.R Spectrum of Metoclopramide Hcl

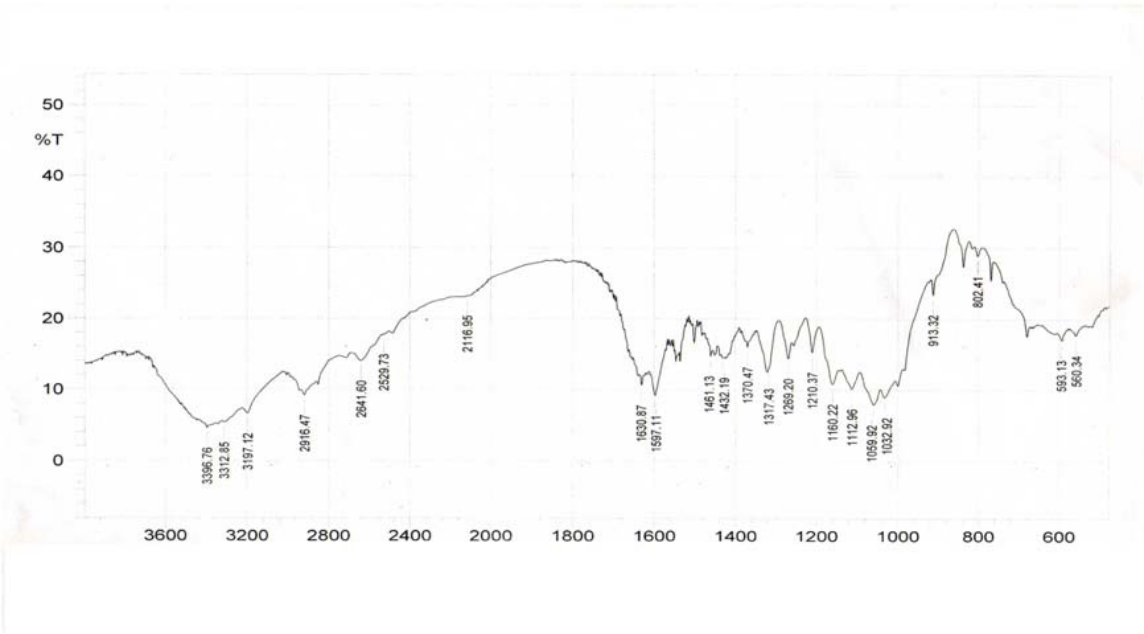


Fig 9 I.R Spectrum of Metoclopramide Hcl + Excipients

Table .12 Characteristics of powder

Parameter's	F_1	F_2	F_3	F_4	F_5	F_6	F_7
Angle of repose, Degrees	24.21	23.35	21.64	23.85	22.85	21.94	22.88
Bulk density,g/cm^3	0.62	0.66	0.42	0.53	0.52	0.56	0.52
Tapped Density,g/cm^3	0.71	0.72	0.55	0.62	0.62	0.66	0.63
% compressibility	14.51	10.65	23.63	14.51	16.12	15.15	17.46
Hausner ratio	1.14	1.2	1.30	1.17	1.19	1.17	1.21
Hardness, Kg/cm^2	5.8	6.1	6.4	6.2	5.7	5.9	6.6
Thickness , mm	3.17	3.30	3.25	3.40	3.15	3.16	3.20
% Friability	0.28	0.24	0.12	0.36	0.35	0.18	0.25
Weight variations	2.4	2.5	2.4	2.6	2.6	2.6	2.3
% Metoclopramide Hcl	96.89	96.42	96.82	100.10	98.77	98.22	98.99

Table 13 -Dissolution profile of all batches

Time(hrs)	Percent cumulative drug released (Mean ± S.D)						
	Formulation code						
	F1	F2	F3	F4*	F5	F6	F7
1	23.31 ± 0.73	28.34 ±0.96	25.15 ±1.24	14.14 ±0.80	31.32 ±1.28	42.71 ±0.51	31.45 ±1.21
2	31.25 ±0.46	34.12 ±1.12	32.45 ±0.42	23.15 ±1.06	41.98 ±1.56	48.57 ±1.25	38.41 ±0.76
4	42.53 ±0.29	46.91 ±0.22	41.17 ±0.80	42.57 ±1.49	45.63 ±0.78	52.71 ±0.46	47.69 ±1.27
6	56.17 ±0.95	51.19 ±0.49	55.91 ±1.57	60.17 ±0.77	54.13 ±0.39	58.65 ±2.51	62.79 ±0.98
8	72.37 ±1.31	61.16 ±1.18	59.70 ±1.49	79.37 ±0.93	60.28 ±2.65	64.31 ±1.22	71.24 ±1.37
10	89.37 ±0.65	67.34 ±0.80	63.54 ±0.47	92.37 ±1.25	69.47 ±0.85	71.23 ±0.58	78.23 ±0.69

Conclusion :

From these data it is concluded that Mannitol and Hydroxy methyl propyl cellulose improve the release of the drug in F-4 Formulation as compared to F-1, F-2,F-3 ,F-5,F-6 and F-7 .

Comparative graph of the formulations (F-1 to F-7) of MetoclopramideHydrochloride

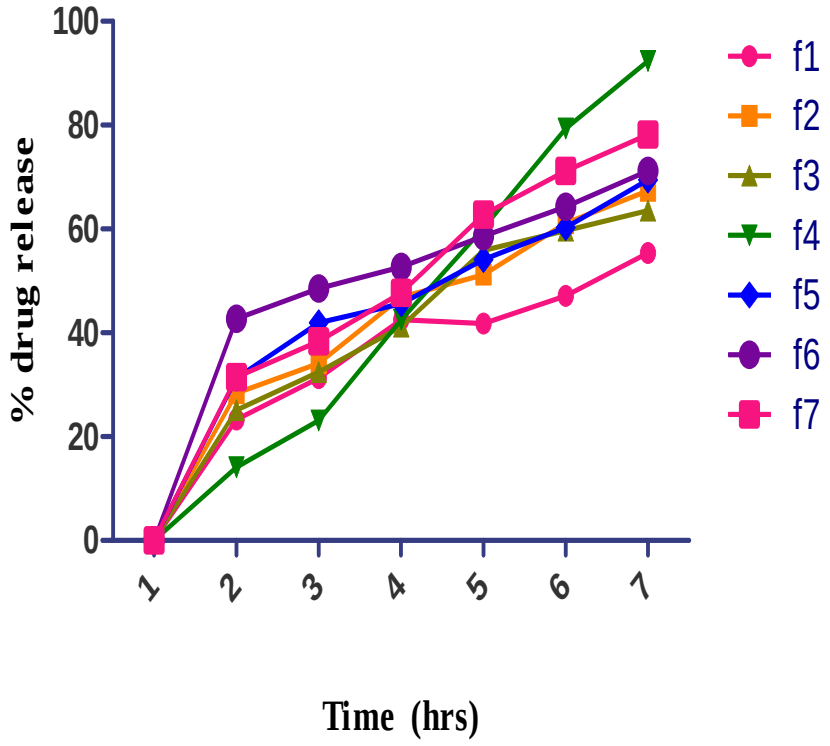


Fig 10Dissolution profile of metoclopramide HCL

Table . 14Kinetic modeling of MCP release from different formulations (F-1 to F7)

Formula no.	Zero order model R	Higuchi diffusion model R
F1	0.942	0.996
F2	0.940	0.994
F3	0.961	0.992
F4	0.994	0.999
F5	0.978	0.989
F6	0.968	0.990
F7	0.953	0.993

r = correlation coefficient

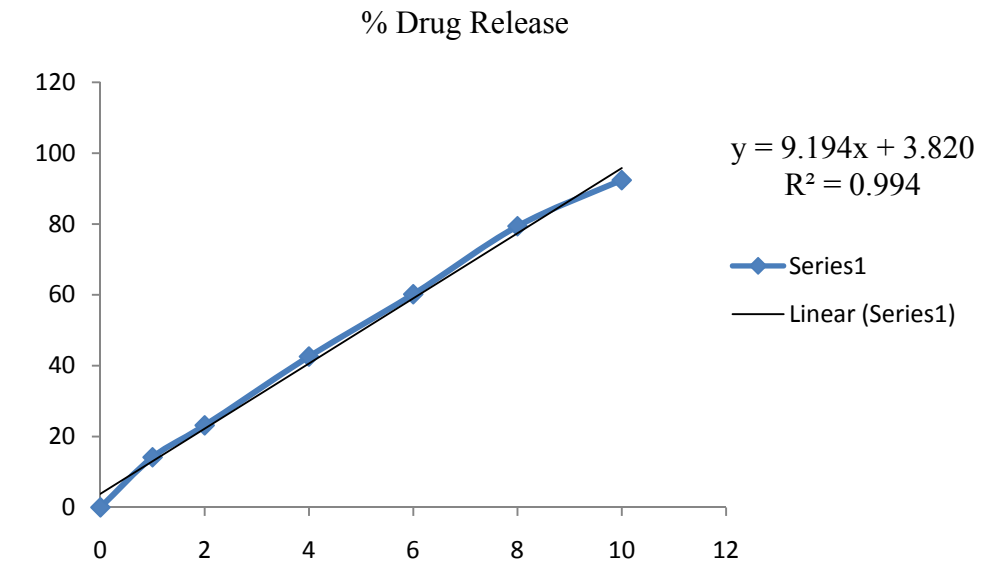


Fig 11KINETIC TREATMENT DISSOLUTION PROFILE OF F4 BATCH

(ZEROORDER)

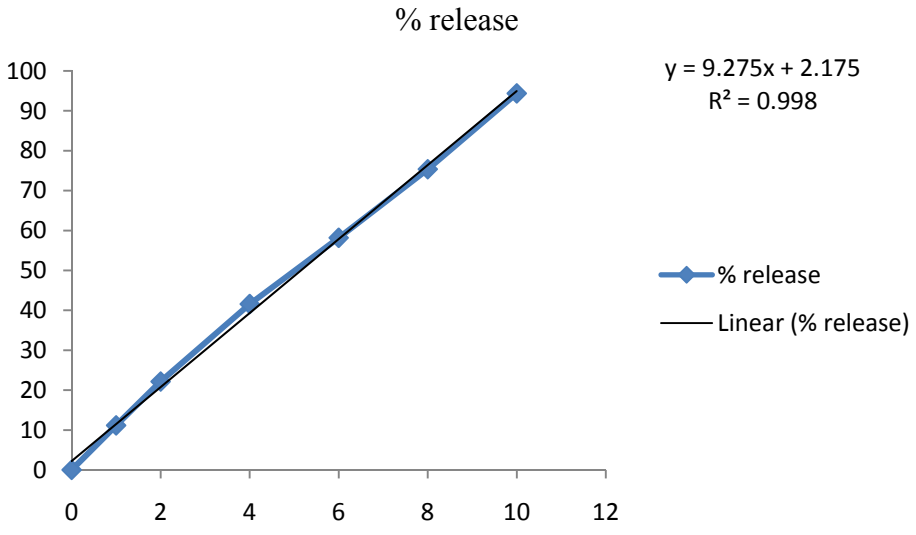


Fig .12 KINETIC TREATMENT DISSOLUTION PROFILE OF F4 BATCH

(HIGUCHI MODEL)

Table .15Stability Parameters of F4 batch stored at room temperature.

Parameters	Initial	After 15 days	After one month
Drug content (%)	100.10	99.15	99.00
% drug release (10hrs)	92.37	92.12	91.90

Table .16 Stability Parameters of F4 Batch stored at 40^0C for 75% RH

Parameters	Initial	After15 days	After one month
Drug Content(%)	100.10	98.90	98.12
% drug release (10hrs)	92.37	91.12	90.90

Conclusion:

Tablets kept for stability studies were examined. The color of the formulation, i.e.F-4 was similar before and after stability studies. Shell texture of the formulation packed in PVC/PVDC (clear) Aluminum Blister pack had no change at 40°C /75%RH ($\pm 2^0$ C/±5RH) after three months. This indicated that the tablets had no effect of moisture from the environment in PVC/PVDC (clear) Aluminum Blister pack.

SUMMARY AND CONCLUSION

In present work attempts have been made to formulate sustaintedrelase matrix tablet of metoclopramide ,by using hydrophilic polymer ,which is preferable used as anti-emetic .

In present study attempts were made to formulate 202mg sustaindedrelase once daily formulation which can provide effective drug relase for 10 hrs.

Sustained relase matrix tablet of metoclopramide were prepared by direct compression method .in vitro study showed formulation F-4 was well suited to be sustained release formulation.

Matrix tablet were prepared using polymer with HPMC by direct comprssion technique. Metoclopramide meets all the characteristic to formulate in the form of sustained relase drug delivery system.

Under the pre formulation study the organoleptic properties were complied with USP specification .physical properties such as bulk density and tapped density were more in case of granules ready for direct compression.

The compatibility evaluation werepreformed by FT-IR spectroscopy analysis. A study implies that the drug and polymers are compatabile with each other. There were no interaction found between polymers and drug.

The optimized formulation F-4 was evaluated on the basis of pharmacopoeial specification shape of the tablet were round convex disc. The physical parameter like length, width ,thickness,hardness,frability and weight variation is carried out.

Assay was carried out for optimized formulation and the result were found to be 98.19 % by UV.

Stability study were carried out by kepping the tablet at room temp (25c &60%RH) and at accelerated temp (40c and 75 %) in stability chamber for 30 days. The result of stability studies conducted on F-4 reveled no change in physical appearance,drug contain and in vitro dissolution

profile where spectrum obtained no incompatibility ,hence F-4formulation was found to be stable at tested tempreture.

Final selected formulation were found to be zero order drug relase ,governed by diffusion of through swollen matrix and erosion of the matrix ,showing anomalous diffusion of non fickian transport .

From the result obtained ,it can be concluded that formulation F-4 has achieved the objective of sustained drug relase ,patient convenience and cost effectiveness as asingle daily dose of the drug .

Overall it was concluded that for the development of controlled release dosage form for poorly soluble drug ,polymer blends of different grade of HPMC and presence of disintegrants ,which impart the hydrophilic environment and wettability to molecule of drug leads to more uniform drug release,respectively .

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